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SEQUENTIAL COMPARISON OF THERAPY WITH BETA-BLOCKERS AND CALCIUM CHANNEL BLOCKERS WITH CELIPROLOL THERAPY IN PATIENTS WITH ANGINA PECTORIS, HYPERTENSION, OR BOTH

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ABSTRACT

Unlike patients with either hypertension (HT) or angina pectoris (AP) alone, patients with both HT and AP usually have a reduced left ventricular compliance and may, therefore, have an impaired capability to cope with acute hemodynamic changes generated by standard beta-blockers or calcium channel blockers. Celiprolol has been documented to produce fewer adverse effects and equal efficacy compared with standard beta-blockers or calcium channel blockers. We carried out a 16-week open-label, sequential comparison of standard monotherapy versus celiprolol in 172 patients with either HT alone, AP alone, or HT + AP. We compared the effects on symptoms and adverse effects. The occurrence of adverse effects from drug therapy was definitely more common in the HT + AP patients than in patients with AP alone or HT alone. Despite this imbalance in the groups, celiprolol overall produced fewer occurrences of fatigue, dizziness, and edema. Celiprolol controlled AP and HT to the same extent as did standard monotherapy. Our data, although preliminary, suggest that patients with both HT and AP are prone to adverse effects of standard drug therapy, and that celiprolol, while equally effective, is largely devoid of adverse effects as compared with standard therapy, particularly in patients with both HT and AP.

INTRODUCTION

Patients with both hypertension (HT) and coronary artery disease such as angina pectoris (AP) usually have a reduced left ventricular compliance as measured by a prolonged filling time.[1,2] Such properties may impair their capability to cope with the hemodynamic changes generated by beta-blockers and calcium channel blockers. Considering that common adverse

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effects with these drugs such as hypotension, fatigue, and reduced exercise tolerance have been largely attributed to hemodynamic effects,[3–6] we assumed that patients with HT and AP would be prone to adverse effects with standard drug therapy. This has not been tested, however.

Celiprolol is a representative of a new class of selective beta-blockers with vasodilatory $beta_2$-agonistic properties[7] and has been documented to combine lower scores of adverse effects with equal efficacy when compared with standard beta-blockers or calcium channel blockers.[8,9] Celiprolol had not been tested, however, in patients with both HT and AP.

The first objective of this study was to determine whether patients with HT and AP would be prone to adverse effects of standard drug therapy compared with patients with either AP or HT alone. Secondly, we assessed the effects of celiprolol in these three groups of patients.

PATIENTS AND METHODS

Patients and Study Design

We conducted a 16-week, across-group, multicenter comparison of monotherapy with various beta-blockers or calcium channel blockers and monotherapy with celiprolol. Patients were recruited from the outpatient clinics of the cardiology departments of 16 hospitals in The Netherlands. Criteria for qualification were a diagnosis of mild essential hypertension according to the criteria of the Joint National Committee[10] (resting heart rate >140/90 mm Hg and <170/110 mm Hg) or stable angina pectoris (New York Heart Association class I or II, or effort-induced AP). A total of 205 patients not older than 80 years of age were enrolled.

After giving informed consent, all of the patients were treated for 8 weeks with equipotent doses of standard beta-blockers (metoprolol 100 to 200 mg daily in 21 patients, sotalol 40 to 80 mg daily in 40 patients, and atenolol 50 to 100 mg daily in 49 patients) or standard doses of calcium channel blockers (nifedipine 20 to 30 mg daily in 32 patients and diltiazem 60 to 120 mg daily in 21 patients). The remaining nine patients (5%) were treated with a combination of these beta-blockers and calcium channel blockers using the lowest dosages as mentioned above. The treatment regimens were chosen by the participating cardiologists and were standard for their institutions. After 8 weeks these treatments were replaced by celiprolol 200 to 400 mg once daily in all patients.

Evaluation

Patients were evaluated by their cardiologists at the outpatient clinic

Table I. Patient characteristics.

	HT + AP (n = 47)	AP (n = 92)	HT (n = 33)	*P* Between Groups
Chronic obstructive pulmonary disease (n)	17 (36%)	10 (11%)	2 (6%)	0.0008
Peripheral vascular disease (n)	7 (15%)	14 (15%)	3 (9%)	NS
Hypercholesterolemia (n)	7 (15%)	4 (4%)	2 (6%)	NS
Mean age (y)	69	71	62	NS
Range	40–80	36–80	40–72	
Sex				
Male	34	72	22	NS
Female	13	20	11	NS
Left ventricular hypertrophy (n)	8 (17%)	0 (0%)	7 (21%)	0.001
Ejection fraction* <45% (n)	3 (6%)	8 (9%)	not tested	NS

HT = hypertension; AP = angina pectoris.
* These patients were allowed to continue taking low doses (10 mg daily) of enalapril, an angiotensin-converting enzyme inhibitor.

at baseline and after 8 and 16 weeks of treatment (Table II). Evaluation consisted of a medical history and physical examination, measurements of sitting blood pressure, and an electrocardiogram. Blood pressure was measured (average of three measurements) after 10 minutes of rest, by auscultation with a mercury manometer. The diastolic value was taken as the start of the Korotkoff sounds phase IV. Assessment of adverse effects and symptoms of AP was performed after 8 and 16 weeks of treatment using a questionnaire based on the quality-of-life questionnaire of Bulpitt and Fletcher for patients with HT[11] and the quality-of-life questionnaire of Marquis, Fayol, and Joire for patients with AP.[12] Both of these questionnaires have a negligible within-subject test/retest variability in untreated subjects. The questionnaires were self-administered by the patient after explicit instruction by a test assistant and required about 20 minutes to complete. The test assistant was unaware of the treatments given. All patients were given both questionnaires. Consent for the study was obtained from all of the participating centers' ethics committees.

Table II. Study evaluations.

	Standard Therapy		Celiprolol 200–400 mg od
	Baseline	Week 8	Week 16
Medical history	x	x	x
Physical examination	x	x	x
Sitting blood pressure	x	x	x
Electrocardiogram	x	x	x
Quality of life		x	x

od = once daily.

Statistical Analysis

Data were analyzed using analysis of variance or the chi-square analysis of contingency table with use of the Bonferroni inequality to adjust between-group P values.

RESULTS

Of the 205 patients originally enrolled, 172 were included in the final analysis. Of the 33 that were excluded, 19 were lost to follow-up, 14 during the first 8 weeks of the study, and 14 were excluded because their questionnaires were only partly answered. Characteristics of the remaining 172 patients are shown in Table I. Patients with both AP and HT had a greater incidence of chronic obstructive pulmonary disease at enrollment (HT + AP vs AP alone and HT + AP vs HT alone, both $P = 0.0008$). AP patients had less left ventricular hypertrophy than the HT and HT + AP groups (both $P = 0.001$). Patients with a compromised left ventricular ejection fraction were allowed to continue taking low-dose enalapril 10 mg daily. Other medications that were allowed included aspirin and short-acting nitrates ad libitum.

Table III shows the effects of the two treatment modalities. The effects on diastolic blood pressure and symptoms of AP were similar between the groups. Celiprolol controlled AP to the same extent as did standard therapy. Table IV shows that with both standard therapy and with celiprolol the occurrence of adverse effects was significantly different between the various groups. Multiple comparison analysis confirmed that this was mainly due to a significantly larger number of patients with adverse ef-

Table III. Effects of standard monotherapy* or celiprolol in patients with hypertension (HT) alone, angina pectoris (AP) alone, or HT + AP.

	HT + AP (n = 47)	AP (n = 92)	HT (n = 33)	P Between Groups
Diastolic blood pressure ≤90 mm Hg				
Standard	21 (45%)	—	17 (52%)	NS
Celiprolol	22 (47%)	—	16 (48%)	NS
AP not yet controlled†				
Standard	24 (51%)	47 (51%)	—	NS
Celiprolol	11 (23%)	25 (27%)	—	NS
AP controlled				
Celiprolol better than standard	13 (28%)	22 (24%)	—	
Same	9 (19%)	23 (25%)	—	
Standard better than celiprolol	2 (4%)	2 (2%)	—	NS

* Ninety-five percent of the patients were receiving monotherapy with either a beta-blocker (64%) or a calcium channel blocker (31%); the remaining 5% were receiving combined therapy with a calcium channel blocker plus a beta-blocker.
† Controlled means virtually no AP attacks.

Table IV. Adverse effects of standard monotherapy* or celiprolol in patients with hypertension (HT) alone, angina pectoris (AP) alone, or HT + AP.

	HT + AP (n = 47)	AP (n = 92)	HT (n = 33)	*P* Between Groups
Cold hands/feet				
Standard	23 (49%)	28 (30%)	14 (42%)	0.15
Celiprolol	1 (2%)	13 (14%)	3 (9%)	0.10
Fatigue				
Standard	35 (74%)	33 (36%)	7 (21%)	0.0001
Celiprolol	14 (30%)	20 (22%)	4 (12%)	0.05
Reduced libido				
Standard	19 (40%)	2 (2%)	3 (9%)	<0.0001
Celiprolol	12 (26%)	2 (2%)	3 (9%)	NS
Arrhythmia				
Standard	7 (15%)	10 (11%)	2 (6%)	0.46
Celiprolol	2 (4%)	1 (1%)	2 (6%)	NS
Headache				
Standard	11 (23%)	7 (8%)	3 (9%)	0.02
Celiprolol	5 (11%)	2 (2%)	2 (6%)	NS
Dizziness				
Standard	12 (26%)	7 (8%)	1 (3%)	0.0003
Celiprolol	8 (17%)	3 (3%)	1 (3%)	0.08
Dyspnea				
Standard	13 (28%)	5 (5%)	3 (9%)	0.0015
Celiprolol	10 (21%)	3 (3%)	2 (6%)	0.20
Edema				
Standard	10 (21%)	7 (8%)	1 (3%)	0.02
Celiprolol	3 (6%)	3 (3%)	0 (0%)	0.05

* Ninety-five percent of the patients were receiving monotherapy with either a beta-blocker (64%) or a calcium channel blocker (31%); the remaining 5% were receiving combined therapy with a calcium channel blocker plus a beta-blocker.

fects in the HT + AP group than in either the AP group or HT group. During standard therapy this was true for the variables fatigue ($P < 0.001$), reduced libido ($P < 0.01$), headache ($P < 0.01$), dizziness ($P < 0.02$), edema ($P < 0.02$), and dyspnea ($P < 0.02$), and during celiprolol for fatigue ($P < 0.05$), edema ($P < 0.05$), and dizziness ($P < 0.02$). Despite this imbalance in the groups, celiprolol overall produced significantly better scores for fatigue, dizziness, and edema, whereas in most of the other categories a trend was seen toward better scores with celiprolol as well (Table V).

DISCUSSION

Important indicators for calcium channel blockers and beta-blockers are HT and AP. Although these compounds substantially reduce blood pressure in patients with HT, their effect on blood pressure in patients with AP is little.[13] In addition, patients with both HT and AP have a reduced left ventricular compliance that may impair their ability to cope with hemodynamic changes generated by therapy with these drugs. Therefore, across-group analyses of effects and side effects of these drugs may be

Table V. Adverse effects of therapy with celiprolol versus standard monotherapy* in patients with hypertension (HP) alone, angina pectoris (AP) alone, or HT + AP.

	HT + AP (n = 47)	AP (n = 92)	HT (n = 33)	P Within Group
Cold hands/feet				
Celiprolol better than standard	22 (47%)	15 (16%)	11 (33%)	
Same	1 (2%)	11 (12%)	2 (6%)	
Standard better than celiprolol	0 (0%)	2 (2%)	1 (3%)	0.10
Fatigue				
Celiprolol better than standard	21 (45%)	13 (14%)	3 (9%)	
Same	13 (28%)	17 (18%)	3 (9%)	
Standard better than celiprolol	1 (2%)	3 (3%)	1 (3%)	0.0052
Reduced libido				
Celiprolol better than standard	7 (15%)	0 (0%)	0 (0%)	
Same	12 (26%)	2 (2%)	3 (9%)	
Standard better than celiprolol	0 (0%)	0 (0%)	0 (0%)	NS
Arrhythmia				
Celiprolol better than standard	5 (11%)	9 (10%)	0 (0%)	
Same	2 (4%)	1 (1%)	1 (3%)	
Standard better than celiprolol	0 (0%)	0 (0%)	1 (3%)	0.16
Headache				
Celiprolol better than standard	6 (13%)	5 (5%)	1 (3%)	
Same	5 (11%)	2 (2%)	2 (6%)	
Standard better than celiprolol	0 (0%)	0 (0%)	0 (0%)	0.24
Dizziness				
Celiprolol better than standard	4 (9%)	4 (4%)	0 (0%)	
Same	7 (15%)	3 (3%)	1 (3%)	
Standard better than celiprolol	1 (2%)	0 (0%)	0 (0%)	0.07
Dyspnea				
Celiprolol better than standard	3 (6%)	2 (2%)	1 (3%)	
Same	10 (21%)	2 (2%)	1 (3%)	
Standard better than celiprolol	0 (0%)	1 (1%)	1 (3%)	0.18
Edema				
Celiprolol better than standard	7 (15%)	4 (4%)	1 (3%)	
Same	3 (6%)	3 (3%)	0 (0%)	
Standard better than celiprolol	0 (0%)	0 (0%)	0 (0%)	0.008

* Ninety-five percent of patients were receiving monotherapy with either a beta-blocker (64%) or a calcium channel blocker (31%); the remaining 5% were receiving combined therapy with a calcium channel blocker plus beta-blocker.

clinically relevant, but it has drawn little attention from investigators so far. The current study is a preliminary effort to address this issue.

Beta-blockers and calcium channel blockers are routinely prescribed, either separately or in combination, for patients with HT or AP. Calcium channel blockers inhibit calcium ion (Ca^{++}) influx through calcium channels in the cells, thus inducing vasodilation and chronotropic effects. Beta-blockers act on Ca^{++} channels indirectly by inactivating cyclic adenosine monophosphate–dependent protein kinase, which phosphorylates calcium subunits, and thereby results in a decrease in the probability of calcium channel opening. So, while both compounds are helpful in inactivating calcium channels, beta-blockers do so more effectively in the heart, leading to bradycardia, and calcium channel blockers do so in the resistance vessels, leading to reduced afterload. Both of these modalities of action lead to

a considerable fall of blood pressure, which is counteracted in the case of beta-blockers by an increase of stroke volume, and in the case of calcium channel blockers by a reflexogenic increase of both heart rate and stroke volume.

The documented deficiency of such mechanisms in patients with both HT and AP[1,2] may be responsible for the presence of a significantly greater incidence of adverse effects from these drugs in patients with HT and AP than in the HT alone and AP alone groups. This would mean that in this category of patients treatment dosages should be carefully titrated and alternative compounds should be considered.

Celiprolol reduces heart rate and cardiac output to a lesser extent than standard beta-blockers,[7] and it causes afterload reduction to a lesser extent than calcium channel blockers without causing reflex tachycardia.[8] These characteristics may partly explain why celiprolol produced fewer adverse effects, particularly in the group with HT and AP. The combination of a low-dose calcium channel blocker and a standard beta-blocker might be as effective as a beta-blocker with vasodilatory effects such as celiprolol, however, there are documented risks in combination therapy of drug interaction causing enhanced possibilities of serious hypotension as well as serious bradycardia.[4–6] Also, combination therapy is less convenient to patients than monotherapy. In our study, unlike other studies, the group of patients with HT and AP was substantial. There are few data in the literature about the prevalence of HT and AP, although HT has been recognized as a major risk factor for coronary artery disease. HT and AP generally are studied by different disciplines. A diagnosis of AP may be deemphasized in HT studies, as may be a diagnosis of HT in AP studies. The actual prevalence of coronary artery disease in hypertensive patients thus may be underestimated.

CONCLUSIONS

Our data need to be confirmed through further study, but they suggest that patients with HT and AP are prone to adverse effects from standard therapy with beta-blockers or calcium channel blockers. This particular category of patients may benefit from treatment with beta-blockers with vasodilatory, beta-agonistic properties, such as celiprolol.

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